Treatment of 27 Postoperative Enterocutaneous Fistulas with the Long Half-life Somatostatin Analogue SMS 201-995

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Twenty-seven patients with postoperative enterocutaneous fistulas were treated with parenteral nutrition and SMS 201-995 (100 μg/8 hours, subcutaneously), a long half-life somatostatin analogue. At the time SMS 201-995 was started, 11 patients had low output fistulas (less than 1000 ml/48 hours), 11 patients had high output fistulas (above 1000 ml/48 hours), and 5 patients had fistulas sitting in large abdominal wall defects. Within 24 hours of treatment, a mean reduction of 55% of the fistula output was observed. Fistula site or output before treatment had no influence on the magnitude of output reduction. Spontaneous closure was achieved in 77% of the patients after a mean of 5.8±2.7 days of treatment with this drug. Two patients died (7.4%). Pain at the injection site was referred by 15% of the patients but no other side effects were observed. Glucose intolerance was not observed. SMS 201-995 has been shown to be very useful in the conservative treatment of enterocutaneous fistulas because of its ability to rapidly reduce fistula output and accelerate spontaneous closure.

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SOMATOSTATIN, A TETRADECAPEPTIDE first discovered by Guillemin et al.[1] and isolated by Brazeau et al.,[2] has a powerful inhibitory action on gastrointestinal endocrine and exocrine secretions. Gastrin, gastric acid, pancreatic juice, bile flow, and intestinal secretions are inhibited by this hormone,[3-7] which also has been shown to inhibit gastrointestinal motility[8] and reduce the venous splachnic flow.[9] For these reasons it has been used with success to treat digestive fistulas.[10] Two major disadvantages of somatostatin are its very short half-life, which makes it madatory to give the drug as a continuous intravenous infusion, and the appearance of glucose intolerance due to its inhibitory effects on the pancreatic insulin secretion. This has furthered the research to find synthetic analogues free from these limitations. The octapeptide SMS 901-225 (Sandostatin®) is one of these analogues; it has a half-life of eight hours and less influence on insulin secretion than somatostatin.[11] In a randomized double-blind study we demonstrated that SMS 201-995 was very effective in reducing small bowel fistula output.[12] Herein we report the clinical results obtained using this peptide in addition to parenteral nutrition and surgery in a series of 27 patients with postoperative enterocutaneous fistulas.

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Patients and Methods

Twenty-seven patients with postoperative enterocutaneous fistulas observed at several hospitals in Barcelona from January 1986 to July 1988 entered the study. Patients in whom there was a high suspicion of fistulas arising on neoplastic tissue or ischemic bowel were not included. All the treatments were supervised by one of us (P.N.C.). There were 18 men and 9 women with a mean age of 57 years (range, 23 to 80 years). The patients had been on conservative treatment with parenteral nutrition for 2 to 98 days (mean, 25 days) before receiving SMS 201-995. The etiology of the fistulas is shown in Table 1. In 60% of cases the fundamental disease was cancer (colon cancer in 11, gastric cancer in 5) but two thirds of these patients developed anastomotic fistulas after small bowel resection was required to treat intestinal obstruction due to adhesions. The origin of the fistula was proved in all cases by fistulography and/or gastrographin or barium meal. All fistulas were stratified according to the classification, based on their anatomy and output, previously reported by our group,[13] which has a prognostic value. According to this classification, at the time treatment with SMS 201-995 was started, 11 patients had type 1a low output fistulas

(less than 1000 cc/48h), 11 had type 1b high output fistulas (more than 1000 cc/24h) and 5 patients had type 2 fistulas sitting on abdominal wall defects. No patient with colocolic or colorectal fistulas (type 3), cervical esophageal, pancreatic, or biliary fistulas were included. Fistula output was measured daily from four days before starting the treatment with SMS 201-995 to the time of fistula closure, reoperation, or death. Time to spontaneous closure was calculated as the time interval between starting treatment and achieving no output whatsoever, although administration of the drug was continued for three additional days. SMS 201-995 was supplied by Sandoz Co. (Basle) in 1 ml ampoules containing 100 μg of SMS 201-995 in saline buffered at a pH 3.9 to 4.5. SMS 201-995 was administered subcutaneously at a dose of 100 μg/8 hours.

Results

SMS 201-995 dramatically reduced fistula output within 24 hours of its administration. A mean reduction of 55% for all fistulas was achieved (62% in high output and 49% in low output fistulas). The magnitude of the fistula output fall was not influenced by the anatomical site or the time elapsed between beginning of treatment and closure. In 21 patients (77.7%) the fistula closed spontaneously in a mean of 5.8±2.7 days. In six patients the fistulas did not close after conservative treatment. One of these patients died of sepsis. The remaining five patients were successfully treated with reoperation; in three of them total disruption of the suture line was appreciated and in two a distal obstruction could explain the failure to close spontaneously. All these six patients had fistulas with outputs greater than 1200 ml/24 hours. In all of them a significant reduction in fistula output was achieved with SMS 201-995, and skin care was very much improved.

Two patients died during the study (7.4%), one of uncontrolled intrabdominal infection and the other of severe pulmonary infection; the latter patient died once his fistula had closed spontaneously. No side effects attributable to the drug were observed. One patient developed significant cholestasis but this was probably secondary to TPN.[14] Another patient who had previously received somatostatin at another institution developed a mild hypersensitivity reaction that could be controlled with oral antihistaminics. Four patients (14.8%) repeatedly complained of pain at the injection site.

Discussion

Since parenteral nutrition became widely available during the mid 1970s, no significant progress has been made in the treatment of enterocutaneous fistulas. Conservative treatment usually succeeds in closing between 60% to 75% of fistulas, although the chances of cure are different according to their anatomy and output.[13] Crohn's disease affecting the fistulous bowel and the presence of uncontrolled sepsis drastically reduce the chances of cure by conservative means.[15] The major inconveniences of medical treatment are its long duration, high costs, and incidences of morbidity related to prolonged hospitalization. We have used the drug SMS 201-995 as a pharmacologic adjunct to standard therapy (parenteral nutrition, skin care, and infection control) with the hope of overcoming some of these problems. This somatostatin analogue has shown two main advantages: first, it reduces fistula output, which facilitates the control of water and electrolyte disturbances and skin care; second, when anatomically possible, spontaneous closure can usually be obtained in three to ten days. The acceleration of spontaneous healing has also been observed with the native somatostatin, as shown in Table 2, in which the existing experience on small bowel fistulas with this hormone is summarized. While spontaneous closure with parenteral nutrition alone is usually obtained after a mean of 3 to 5 weeks, the addition of SMS 201-995 has resulted in a very substantial shortening of hospitalization, which may have important implications for patient care in terms of cost, rate of morbidity, and quality of life. In Table 3 we compare the results of treatment of gastrointestinal fistulas, stratified according to its severity, before and after the use

TABLE 1. *Etiology of Postoperative Fistulas in 27 Patients*

Etiology	Cases
Anastomotic leakage after small bowel resection	14
Adhesions/Bowel necrosis	12
Strangulated hernia	1
Crohn's disease	1
Trauma due to foreign body	3
Billroth I leakage	3
Suture dehiscence after penetrating abdominal trauma	2
Pyloroplasty leakage	2
Duodenal stump leakage	2
Choledochoduodenostomy leakage	1

TABLE 2. *Spontaneous Closure Rates and Mean Closure Time of Enterocutaneous Fistulas Treated with Parenteral Nutrition and Native Somatostatin*

Author	Year	n	Spontaneous Closure (%)	Time to Closure (days)
Frerker	1981	19	—	—
Hild	1982	16	81.2	16.1
Costanzo	1982	6	85.1	1
Costanzo	1984	12	75	2.3
Jost	1984	39	74.6	7
Angelini	1984	5	60	7
Bassi	1985	12	91.6	7
Pederzoli	1986	8	87.5	6.6
Constanzo	1987	37	78.3	5.4
Hernandez	1988	8	75	13
Total		175	78.4	7.2

TABLE 3. *Results of Conservative Treatment of Enterocutaneous Fistulas Stratified According to Its Severity*

	Type of Fistula	Spontaneous Closure	Mortality Rate (%)
Without SMS[13]	1 (n = 61)	48 (79%)	18
	1a (n = 35)	34 (97%)	6
	1b (n = 26)	14 (54%)	32
	2 (n = 14)	1 (7%)	60
With SMS (Present series)	1 (n = 22)	21 (95%)	4.3
	1a (n = 11)	11 (100%)	0
	1b (n = 11)	10 (91%)	9
	2 (n = 5)	0	25

of SMS 201-995. The most encouraging results have been obtained in patients with 1b, high-output fistulas. In our previous experience, only 50% of these fistulas were safely managed conservatively (parenteral nutrition and sepsis drainage without a direct attempt at fistula closure), while with the use of SMS 201-995 as many as 90% closed spontaneously.

The drastic reduction in fistula output observed shortly after the administration of SMS 201-995[12] can be tentatively explained through two different mechanisms. The first would involve a direct inhibition of gastrointestinal, biliary, and pancreatic secretions and the second would involve the relaxation of the bowel muscle layer with accumulation of fluid within the bowel lumen. After cessation of treatment, in patients who ultimately required surgical treatment, fistula output returned to the pretreatment levels. The rebound effect (fistula output greater after cessation of treatment than before treatment), seen with native somatostatin has not been observed after SMS 201-995 administration,[17] probably because this drug is more resistant to plasma proteolytic enzymes and its activity diminishes more gradually. Finally, SMS 201-995 seems also to offer advantages from the point of view of carbohydrate metabolism. This peptide has a lesser inhibiting effect on insulin secretion than somatostatin[11] and this is probably the reason why we have not observed hyperglycemia despite the fact that all our patients were on parenteral nutrition.

In summary, our experience indicates that SMS 201-995 is a very promising drug that represents a significant advance in the conservative treatment of postoperative enterocutaneous fistulas because it rapidly reduces fistula output and shortens the spontaneous closure time.

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